IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Ray W. WOOD et al.
Title:	NANOPARTICULATE BECLOMETHASONE COMPOSITIONS (AS AMENDED)
Appl. No.:	10/667,472
Filing Date:	09/23/2003
Examiner:	Mina Haghighatian
Art Unit:	1616
Confirmation Number:	9063

REPLY BRIEF

Mail Stop Appeal Brief - Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Under the provisions of 37 C.F.R. § 41.39, Appellants are filing this Reply Brief in response to the Examiner's Answer (the "Answer"), dated December 28, 2006. As the deadline for response is February 28, 2007, this paper is timely filed.

Appellants are requesting an oral hearing, and to that end, Appellants submit with this reply a Request for Oral Hearing and the fee prescribed by 37 C.F.R. § 41.20(b)(3).

Table of Contents

I. THERE IS NO *PRIMA FACIE* CASE OF OBVIOUSNESS

U.S. Patent No. 5,145,684 to Liversidge *et al.* ("Liversidge") in view of Lacy *et al.*, DRUG INFORMATION HANDBOOK pp,. 95-96 (Lexi-Comp, Inc. 1993) ("DIH") does not render the claimed invention obvious for at least two reasons. First, the examiner has failed to establish a *prima facie* case of obviousness because one of skill in the art would have neither a motivation to combine the references, nor an expectation of success in doing so. The Examiner's proffered motivation amounts to nothing more than an "obvious to try" rationale. Such purported motivation is particularly deficient in view of Liversidge's explicit admonition against simply picking and choosing active agents, which nullifies any expectation of success. Second, even assuming, *arguendo*, that a *prima facie* case of obviousness had been established, the *prime facie* case has been rebutted by a demonstration of unexpected results. The Examiner dismisses the unexpected results as the same as those disclosed by Liversidge, but this is not correct. Liversidge does not teach or suggest the unexpected benefits of using nanoparticulate beclomethasone in a nebulizer, as demonstrated by the present application's working examples.

A. There Is No Motivation To Combine the References

There is no motivation to combine Liversidge and DIH because there is no motivation to select beclomethasone from the thousands of active agents that could potentially be employed with the teachings of Liversidge. Liversidge generally relates to nanoparticles of a crystalline drug substance with a surface modifier absorbed on the surface thereof. In that regard, Liversidge discloses a lengthy list of potentially suitable classes of drug substances, including corticosteroids. Beclomethasone, however, is absent from this lengthy list. DIH, an encyclopedic listing of drugs, discloses beclomethasone along with hundreds of other drugs. Lacking from either of these references is a reason for one of skill in the art to select beclomethasone from among the hundreds of drugs cataloged by DIH and employ it with the teachings of Liversidge.

The Examiner proffers the following motivation to select beclomethasone from DIH and use beclomethasone with the teachings of Liversidge:

> It would have been obvious to a person of ordinary skill in the art at the time the invention was made, given the general formulations of Liversidge on formulations containing active agents including corticosteroids, to have looked in the art for other specific species of corticosteroids suitable for formation of compositions, as disclosed in Drug Information Handbook, with reasonable expectations of successfully preparing formulations comprising different active agents for treating different disorders.[1]

In other words, because Liversidge listed corticosteroids as a class of drugs, a skilled artisan would scour the literature and form nanoparticulate forms of every corticosteroid, including beclomethasone.

This purported motivation is deficient, however, because it fails to explain why one of skill in the art would be motivated to select beclomethasone from the myriad of drugs. It is not enough for the prior art to disclose beclomethasone as a corticosteroid, because "[s]ome motivation to select the claimed species ... must be taught by the prior art."[2] *See also In re Deuel*, 51 F.3d at 1558-59, 34 USPQ2d 1210, 1215 ("No particular one of these DNAs can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared"). Here, the prior art lacks such a motivation to select beclomethasone from among many known corticosteroids.

The Examiner tries to establish a motivation to select beclomethasone from among the many known corticosteroids by noting that "beclomethasone is a widely used corticosteroid and has been prepared in powder formulations for inhalation." Answer at 6. Based on this knowledge, the Examiner contends that "one of ordinary skill in the art would be motivated to look into those corticosteroids that have been used and are well known for their properties and functions in then same field." *Id.*

---

[1] Answer at 4; Office Action mailed October 11, 2005 at 4.

[2] MPEP § 2144.08(II)(A)(4)(a).

Again, this rationale does not provide a reason to select beclomethasone to use with the teachings of Liversidge. Simply because beclomethasone "was widely used" does not provide a reason to specifically select it for use in Liversidge's teachings. Similarly, the knowledge of powder forms of beclomethasone for inhalation does not provide any reason to select beclamethasone to use with the teachings of Liversidge. This is especially true in view of Liversidges warning that "not every combination of surface modifier and drug substance provides the desired results [of a stable nanoparticulate composition]."[3] The absence of motivation is underscored by the argument that a skilled artisan would "look into those corticosteroids that have been used and are well known for their properties and functions in then same field." In other words, according to the Examiner, one of skill in the art would been motivated to use all "well known" corticosteroids in combination with Liversidge. Such an argument is the epitome of the proscribed "obvious to try" rationale.

Finally, the Examiner argues that "one of ordinary skill in the art can immediately envision a selection [of beclomethasone] form the class of corticosteroids, since beclomethasone dipropionate is a well known and widely used member of this class." Answer at 7. However, this argument fails for at least two reasons.

First, "[t]o establish a *prima facie* case of obviousness in a genus-species chemical composition situation, as in any other 35 U.S.C. 103 case, it is essential that Office personnel find some motivation or suggestion to make the claimed invention in light of the prior art teachings." MPEP § 2144.08(II)(A); *In re Brouwer*, 77 F.3d 422, 425, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996). Because such motivation is lacking for the reasons discussed above, there is no *prima facie* case of obviousness.

In addition, MPEP § 2144.08(II)(A)(4)(a)-(f) provides factors to consider in assessing the obviousness of a species when the genus is known in the art. Each of the enumerated factors militates against a finding of obviousness, as discussed below.

The size of the genus should be considered, but "size alone cannot support an obviousness rejection." MPEP § 2144.08(II)(A)(4)(a). In fact, "[t]here is no absolute

---

[3] Liversidge, col. 7, lines 21-23.

correlation between the size of the prior art genus and a conclusion of obviousness." *Id.*; *In re Baird*, 16 F.3d 380, 383, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). Here, the genus is neither small nor bound by common properties. Liversidge discloses a lengthy list of classes of drugs with each class covering a variety of drugs with differing physicochemical properties. Even if the genus were considered limited to corticosteroids, there are many corticosteroids, and these different corticosteroids have differing physicochemical properties. Because the class of corticosteroids is large and the physicochemical properties of corticosteroids differ, the size of the genus undercuts any purported motivation to specifically select beclomethasone.

"If the prior art reference expressly teaches a particular reason to select the claimed species or subgenus, Office personnel should point out the express disclosure which would have motivated one of ordinary skill in the art to select the claimed invention." MPEP § 2144.08(II)(A)(4)(b). For example, art recognized equivalence should be identified. *Id.* The Examiner has not identified "a particular reason" and chooses to premise motivation on the generally knowledge that "beclomethasone is a widely used corticosteroid and has been prepared in powder formulations for inhalation." Such a general knowledge does not constitute an express teaching or "a particular reason." The failure to identify "a particular reason" in the references relied upon is not surprising, because the references do not contain such a teaching. Although Liversidge discloses a specific species of steroid, beclomethasone is not expressly taught. The differences between beclomethasone and that of Steroid A are such that one of ordinary skill in the art would not find it obvious to substitute one for the other. In fact, Steroid A is not a clinically approved drug. Instead, it is merely an experimental compound. Thus, one of skill in the art would have no reason to expect Steroid A to be equivalent to beclomethasone in clinical indications, dosage, and physicochemical properties. Accordingly, motivation cannot be found in the express teachings of the references.

The structural similarities between any "typical," "preferred," or "optimum" species and the claimed species should be considered. MPEP § 2144.08(II)(A)(4)(c). The references do not teach any "preferred" or "optimum" corticosteroids. Instead, Liversidge merely lists "Steroid A" as a suitable drug substance. Steroid A does not share a high degree of structural similarity with beclomethasone. Indeed, beclomethasone is 9-chloro-11β,17,21-trihydroxy-

16b-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate, and Steroid A is 5α,17α,-1'-(methylsulfonyl)-1'H-pregn-20-yno[3,2-c]-pyrazol-17-ol. Thus, the compounds lack structural similarity.

Common properties and uses of the prior art species to the claimed species should also be considered. MPEP § 2144.08(II)(A)(4)(d). Here, Steroid A is merely an experimental compound. Thus, one of skill in the art would have no reason to believe that Steroid A and beclomethasone have similar clinical indications, dosages, routes of administration, and physicochemical properties, nor has the Examiner made such an argument. Thus, the compounds do not have any common properties that would motivate a skilled artisan to substitute one for the other.

The predictability of the technology should be considered, because "[i]f the technology is unpredictable, it is less likely that structurally similar species will render a claimed species obvious." MPEP § 2144.08(II)(A)(4)(e). Thus, "it may not be reasonable to infer that they would share similar properties." *Id.* As noted in Section II, Liversidge warns against indiscriminate selection of drugs by teaching that "not every combination of surface modifier and drug substance provides the desired results [of a stable nanoparticulate composition]."[4] In other words, Liversidge warns that it is not predictable what surface modifiers will work with which drugs. Thus, the references weigh against a finding of obviousness.

Second, a genus may be so small that each of the encompassed species are anticipated, but there is no anticipation rejection in this case. MPEP § 2144.08(II)(A)(4)(a); *In re Petering*, 301 F.2d 676, 681, 133 USPQ 275, 280 (CCPA 1962). In addition, this type of rejection is appropriate only where the prior art discloses a small, immediately recognizable class of compounds with common properties. *Id.*; *In re Ruschig*, 343 F.2d 965, 974, 145 USPQ 274, 282 (CCPA 1965). Here, the genus is neither small nor bound by common properties, as discussed above. For example, there are many corticosteroids, and these

[4] Liversidge, col. 7, lines 21-23.

different corticosteroids have differing physicochemical properties and differing clinical indications, dosages, and routes of administration.

B. One Of Skill In The Art Would Have No Expectation Of Success In Combining Liversidge With DIH

Even if there were some motivation to combine Liversidge with DIH, one of skill in the art would not have a reasonable expectation of success. Liversidge warns against indiscriminate selection of drugs by teaching that "not every combination of surface modifier and drug substance provides the desired results [of a stable nanoparticulate composition]."[5] Liversidge's working examples highlight this uncertainty by demonstrating that certain combinations of surface modifiers and drug substances fail to result in stable, nanoparticulate compositions.[6] Such demonstrated failures deprive one of skill in the art from enjoying any reasonable expectation of success and offer, at best, a hope for success.

The Examiner argues that Liversidge's admonitions against indiscriminate selection of drugs "are not commensurate with the scope of the claims," because the claims are not restricted to particular surface modifiers. Answer at 6. But this argument is inapposite. Applicants disclosure demonstrates that a variety of surface modifiers can be successfully used with beclamethasone to form nanoparticulate compositions, but the present application is not prior art. In other words, one of skill in the art did not have the present specification as guidance. Instead, one of skill in the art had the teachings of the prior art, such as Liversidge. The prior art taught that "not every combination of surface modifier and drug substance provides the desired results [of a stable nanoparticulate composition]" and corroborated these teachings with actual reports of failure. Based on the prior art teachings, one of skill in the art would not have a reasonable expectation of success in randomly choosing beclomethasone from among the many known drugs.

---

[5] Liversidge, col. 7, lines 21-23.

[6] *See* Liversidge, Comparative Examples A-F (cols. 14-15).

II. APPELLANTS' UNEXPECTED RESULTS REBUT ANY *PRIMA FACIE* CASE OBVIOUSNESS

Appellants rebutted any *prima facie* case by showing unexpected results. Specifically, Example 1 of the specification describes the preparation of a nanoparticulate beclomethasone composition, as claimed, and compares it to a conventional beclomethasone composition.[7] The specification states that "only about 7% of the [beclomethasone] presented as a suspension or raw drug substance reaches the impactor."[8] On the other hand, "the use of nanoparticles led to a significantly higher fraction reaching the impactor."[9] In addition, a greater fraction of beclomethasone remained in the nebulizer when raw drug substance rather than the nanoparticulate form was used.[10] Thus, the experimental results demonstrate that the nanoparticulate form of beclomethasone results in less waste and more effective delivery. This result was not expected from the prior art and rebuts a *prima facie* case of obviousness.

The Examiner dismisses these unexpected results, because "the advantage of nanoparticles, especially surface modified has been discovered by Liversidge." Answer at 7. The Examiner notes that Liversidge teaches that its nanoparticles are "are stable and do not flocculate or agglomerate due to interparticle attractive forces and can be formulated into pharmaceutical compositions exhibiting unexpectedly high bioavailability (see col. 3, lines 15-31)." *Id.*

While Liversidge does teach that its nanoparticles are stable and result in high bioavailability, these unexpected results are not the same as those demonstrated in the present application. The present application shows that its nanoparticulate beclomethasone was more efficient in reaching the impactor and leaving the nebulizer. Thus, the nanoparticulate form of beclomethasone results in beclomethasone delivery to the body with less waste and more effective delivery. The high bioavailability discussed by Liversidge refers to the bioavailability of drug once it is inside the body rather than its efficiency in reaching the

---

[7] Spec. at page 18, line 17 – page 24, line 4.

[8] Spec. at page 21, lines 27-28.

[9] *Id.* at page 21, lines 29-30.

[10] *See* Table II, col. 4 (page 23); spec. at page 21, lines 14-26.

body. The fact that Liversidge teaches the stability of nanoparticles, *i.e.*, the lack of agglomeration and flocculation, also does not suggest the unexpected results of the claimed invention, because such a property does not suggest that nanoparticulate beclomethasone could be delivered to the body more efficiently, as demonstrated by the present application. Thus, while Liversidge teaches advantages of nanoparticulate drugs in general, it does not suggest the unexpected properties of nanoparticulate beclomethasone disclosed by the present application.

III. CONCLUSION

The rejection of claims 10-22 and 24-26 under 35 U.S.C. § 103(a) as allegedly obvious over Liversidge in view of DIH is untenable because a *prima facie* case of obviousness has not been established. Indeed, the prior art lacks a motivation to arrive at the claimed invention, and the prior art belies any expectation of success. Even if a *prima facie* case of obviousness had been established, Appellants have rebutted that case by demonstrating unexpected results. Thus, Appellants respectfully request that the Examiner's rejection be reversed.

Respectfully submitted,

Date February 27, 2007

By _____ 59,987

FOLEY & LARDNER LLP
Customer Number: 31049
Telephone: (202) 672-5538
Facsimile: (202) 672-5399

Telephone: (202) 295-4758
Facsimile: (202) 672-5399

Michele M. Simkin
Attorney for Applicant
Registration No. 34,717

Shaun R. Snader
Attorney for Applicant
Registration No. 59,987